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Hemodialysis with high-calcium dialysate impairs cardiac relaxation

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Hemodialysis with high-calcium dialysate impairs cardiac relaxation.

Background. During hemodialysis (HD), serum ionized calcium is directly related to the dialysate calcium concentration. We have recently shown an acute induction of hypercalcemia to impair left ventricular (LV) relaxation. In the current study we sought to establish whether changes in serum Ca^{++} also affect LV function during HD.

Methods. We echocardiographically examined the LV relaxation and systolic function of 12 patients with end-stage renal disease before and after three HD treatments with dialysate Ca^{++} concentrations of 1.25 mmol/liter ($dCa^{++}1.25$), 1.5 mmol/liter ($dCa^{++}1.50$), and 1.75 mmol/liter ($dCa^{++}1.75$), respectively. Age- and sex-matched healthy controls were also examined echocardiographically.

Results. The LV posterior wall thickness and the interventricular septum thickness, and the LV end-diastolic dimension and the end-systolic dimensions were significantly greater in the patients when compared with the controls, and the LV fractional shortening, the ratio of peak early to peak late diastolic velocities (E/A_{max}), and the isovolumic relaxation time (IVRT) showed impairment of LV relaxation and systolic function in the patients. Serum ionized calcium increased significantly during the $dCa^{++}1.5$ HD (1.24 ± 0.10 vs. 1.34 ± 0.06 mmol/liter, $P = 0.004$) and $dCa^{++}1.75$ HD (1.19 ± 0.10 vs. 1.47 ± 0.06 mmol/liter, $P = 0.002$), and plasma intact parathyroid hormone decreased significantly during the $dCa^{++}1.75$ HD (medians 8.2 vs. 2.7 pmol/liter, $P = 0.002$). LV systolic function was not altered during any of the treatments. The changes in E/A_{max} and IVRT suggested impairment of relaxation during all sessions, but only during the $dCa^{++}1.75$ HD was the impairment statistically significant (E/A_{max} 1.153 ± 0.437 vs. 0.943 ± 0.352, $P < 0.05$; IVRT 147 ± 29 vs. 175 ± 50 msecond, $P < 0.05$).

Conclusion. HD with high-calcium ($dCa^{++}1.75$ mmol/liter) dialysate impairs LV relaxation when compared with lower calcium dialysate ($dCa^{++}1.25$ and $dCa^{++}1.5$ mmol/liter) treatments.

Key words: hypercalcemia, left ventricle, cardiac systolic function, chronic renal failure.

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The changes in cardiac preload, blood pressure, heart rate, and blood chemistry that take place during a hemodialysis (HD) session are an enormous stress to cardiac function. Additionally, patients with end-stage renal disease (ESRD) often have left ventricular (LV) hypertrophy and systolic as well as diastolic dysfunction [1–8]. Together, this explains the high prevalence of cardiovascular instability during HD treatment.

Studies on the effects of HD on LV systolic function have yielded contradictory results [9–15], whereas several studies have proved HD procedure to impair LV diastolic filling [13–16]. Cardiac preload has been shown to strongly affect the Doppler indices of LV filling [16, 17], but it is most likely not the only determinant of LV relaxation during HD treatment.

During HD, serum-ionized calcium varies directly with the dialysate Ca^{++} concentration, and changes in serum calcium suppress or stimulate the secretion of parathyroid hormone (PTH) [18, 19]. Calcium has an essential role in the contraction and relaxation of cardiac myocyte [20], and PTH affects the cardiac cytosolic calcium homeostasis [21, 22]. We have recently shown that the acute induction of hypercalcemia by calcium infusion impairs LV relaxation [8]. This finding prompted us to study whether corresponding changes in serum concentration of ionized calcium induced by HD affect LV relaxation. In this study, we echocardiographically examined the effect of different serum calcium concentrations on LV relaxation and systolic function during HD treatment by performing three dialysis treatments, each with a different dialysate Ca^{++} concentration.

METHODS

The study group consisted of 12 ESRD patients (10 males, 2 females) undergoing regular HD three times a week, four to five hours per session. The age of the patients ranged from 24 to 76 (median 56) years, and the patients had been in HD treatment from 1 to 41 (median 13) months. The causes of ESRD were diabetic

nephropathy ($N = 4$), chronic glomerulonephritis ($N = 3$), hypertensive nephrosclerosis ($N = 2$), secondary amyloidosis ($N = 1$), polycystic ($N = 1$), and hypoplastic ($N = 1$) kidney diseases. Two patients had congestive heart disease, eight were hypertensive, and four had myocardial infarction in their medical histories. An electrocardiogram taken before the study proved all patients to be in sinus rhythm. Eight patients were receiving β blockers, three calcium antagonists, three angiotensin-converting enzyme inhibitors, five nitrate agents, and four took diuretics. All patients were taking vitamin B and C substitutions, seven calcium-containing phosphate binders, and five took a vitamin D analogue. Six patients were treated with erythropoietin. All patients continued their medication unchanged throughout the study.

During the study period of three weeks, all patients underwent three study HD sessions on the same day of the week two days after the preceding normal dialysis. During these three study days, different dialysate calcium concentrations were used as follows: On the first day, the dialysate Ca^{++} concentration was 1.25 mmol/liter ($dCa^{++}1.25$); on the second day, 1.75 mmol/liter ($dCa^{++}1.75$); and on the third day, 1.50 mmol/liter ($dCa^{++}1.50$). Except for the concentration of calcium, the compositions of the three dialysates were comparable. On the study days, the dialysate flow was 500 ml/min, and the average blood flow was 280 ± 50 ml/min. The other dialyses between the study days were carried out according to patients' routine dialysis program, the dialysate Ca^{++} concentration being 1.50 mmol/liter for 11 patients and 1.25 mmol/liter for 1 patient.

Before and immediately after the three HD sessions, each patient was studied by cardiac echocardiography. At the beginning and the end of HD, blood pressure was measured and blood samples were collected for the measurement of ionized calcium, phosphate, intact PTH, sodium, potassium, creatinine, urea, hemoglobin, magnesium, pH, and bicarbonate. The concentration of serum-ionized calcium was measured with a Radiometer ICA-1 Analyzer (Radiometer A/S, Copenhagen, Denmark). The concentration of intact PTH in the plasma was determined by two-site immunoradiometry (N-tact® PTH IRMA; Incstar Corp., Stillwater, MN, USA). Other laboratory analyses were made by routine automatic methods.

All echocardiographic examinations were made by one investigator (V.K.V.) in a blinded fashion with the investigator not being aware of the dialysate Ca^{++} concentration used. A System FiVe 1.3 ultrasound system (Vingmed Sound AIS, Horten, Norway) equipped with a 2.5 MHz transducer was used. Standard M-mode measurements of the LV were obtained from the parasternal long-axis view, the cursor being placed immediately below the mitral valve tips. The LV end-diastolic dimension (LVEDD) and the thickness of the interventricular septum and the posterior wall was measured at the onset of the electrocardiographic Q wave. The LV end-systolic dimension (LVESD) was measured at the time of the smallest LV diameter. LV fractional shortening (FS) was defined as (LVEDD − LVESD) × 100/LVEDD. The mitral inflow velocity was measured in the apical four-chamber view. The sample volume was placed at the tips of the mitral valve leaflets, whereby the Doppler beam direction was aligned parallel to the expected direction of the ventricular inflow. The following indices were measured: peak early diastolic velocity (E_{max}), peak late diastolic velocity (A_{max}), and the E/A_{max} ratio. The isovolumic relaxation time (IVRT) was measured as the time from closure of the aortic valve to the onset of mitral valve opening and the deceleration time (DT) as the time from the peak to the end of the E wave.

The control group consisted of age- and sex-matched healthy subjects who were also echocardiographically examined. All patients gave informed consent, and the study was approved by the Ethics Committee of Tampere University Hospital.

Statistical methods

The means and standard deviations of all variables were calculated. The Wilcoxon signed-ranks test for paired samples, the Mann–Whitney U-test, a simple regression, and a multiple regression analysis with forward variable selection were used to determine statistical significance, and P values of less than 0.05 were considered significant. The Statgraphics® (version 7.0) statistical package was used (Manugistics, Inc., Rockville, MD, USA).

RESULTS

Clinical findings

The predialysis and postdialysis values of systolic, diastolic, and mean arterial blood pressures, heart rate, body weight, and total ultrafiltration (UF) are shown in Table 1. Both the predialysis and the postdialysis values and the dialysis-induced changes of all these parameters were comparable between the different dialysis sessions. During the $dCa^{++}1.75$ HD, systolic and mean arterial blood pressure tended to rise, but the changes were not statistically significant.

Laboratory findings

The laboratory values measured before and after the three different HD procedures are shown in Table 2. Mean serum-ionized calcium was within the normal range at the beginning of each dialysis session, and there were no differences in the predialysis values of serum-ionized calcium or plasma intact PTH between the sessions. During the $dCa^{++}1.25$ dialysis, serum-ionized calcium tended to decrease (1.20 ± 0.11 vs. 1.17 ± 0.08

Table 1. Clinical data on the 12 patients before (pre) and after (post) the three dialysis procedures

	Dialysate Ca^{++} 1.25 mmol/liter		Dialysate Ca^{++} 1.5 mmol/liter		Dialysate Ca^{++} 1.75 mmol/liter	
	pre	post	pre	post	pre	post
Systolic BP *mm Hg*	151 ± 18	151 ± 27	150 ± 31	157 ± 20	151 ± 23	164 ± 31
Diastolic BP *mm Hg*	87 ± 8	84 ± 13	90 ± 13	89 ± 12	88 ± 15	88 ± 16
Mean arterial BP *mm Hg*	119 ± 11	118 ± 18	121 ± 21	123 ± 16	119 ± 17	126 ± 21
Heart rate *beats/min*	71 ± 12	77 ± 16[a]	71 ± 10	79 ± 12[a]	73 ± 15	79 ± 17[a]
Body weight *kg*	85.0 ± 18.1	82.4 ± 17.1[a]	83.4 ± 18.7	81.5 ± 17.9[a]	84.0 ± 17.6	82.7 ± 17.8[a]
Total ultrafiltration *ml*	2580 ± 1350		2120 ± 2220		2160 ± 2190	

[a] Before vs. after hemodialysis, $P < 0.05$

Table 2. Pre- and postdialysis laboratory data on the three hemodialysis procedures in 12 hemodialysis patients

Laboratory values and the normal ranges	Dialysate Ca^{++} 1.25 mmol/liter		Dialysate Ca^{++} 1.5 mmol/liter		Dialysate Ca^{++} 1.75 mmol/liter	
	pre	post	pre	post	pre	post
Serum ionized calcium *mmol/liter*	1.20 ± 0.11	1.17 ± 0.08	1.24 ± 0.10	1.34 ± 0.06[a,b]	1.19 ± 0.10	1.47 ± 0.06[a,b,c]
Plasma phosphate *mmol/liter*	1.98 ± 0.56	1.01 ± 0.30[a]	2.12 ± 0.71	1.10 ± 0.35[a]	1.95 ± 0.75	1.08 ± 0.36[a]
Plasma intact PTH *pmol/liter*	5.0 (median)	7.2 (median)	8.4 (median)	4.8 (median)[b]	8.2 (median)	2.7 (median)[a,b,c]
Plasma magnesium *mmol/liter*	0.97 ± 0.11	0.85 ± 0.06[a]	0.97 ± 0.15	0.84 ± 0.08[a]	0.96 ± 0.13	0.84 ± 0.06[a]
Blood hemoglobin *g/liter*	113 ± 8	119 ± 14[a]	112 ± 14	119 ± 13[a]	113 ± 12	118 ± 15[a]
Plasma sodium *mmol/liter*	142 ± 3	143 ± 2	142 ± 4	143 ± 1	142 ± 3	143 ± 1
Plasma potassium *mmol/liter*	5.0 ± 0.7	3.6 ± 0.4[a]	4.7 ± 0.7	3.8 ± 0.4[a]	4.7 ± 0.6	3.7 ± 0.3[a]
Plasma chloride *mmol/liter*	102 ± 4	99 ± 2[a]	102 ± 5	100 ± 2	102 ± 5	100 ± 2
Plasma creatinine *μmol/liter*	776 ± 310	348 ± 160[a]	755 ± 293	346 ± 144[a]	737 ± 288	335 ± 141[a]
Serum urea *mmol/liter*	21.9 ± 4.2	8.0 ± 2.7[a]	20.0 ± 5.0	7.5 ± 2.4[a]	20.0 ± 3.5	7.0 ± 1.7[a]
pH	7.37 ± 0.02	7.44 ± 0.05[a]	7.36 ± 0.04	7.45 ± 0.04[a]	7.38 ± 0.04	7.45 ± 0.06[a]
HCO_3 *mmol/liter*	22.5 ± 2.3	28.5 ± 1.2[a]	23.2 ± 2.2	28.8 ± 1.1[a]	23.0 ± 2.5	28.3 ± 1.0[a]

Reference values are: serum ionized calcium (1.15–1.30) mmol/liter), plasma phosphate (0.80–1.40 mmol/liter), plasma intact PTH (1.0–6.8 pmol/liter), plasma magnesium (0.75–1.00 mmol/liter), blood hemoglobin (130–180 g/liter), plasma sodium (135–146 mmol/liter), plasma potassium (3.3–4.8 mmol/liter), plasma chloride (96–111 mmol/liter), plasma creatinine (<115 μmol/liter), serum urea (3.0–8.5 mmol/liter), pH (7.35–7.44), HCO_3 (22.0–27.0 mmol/liter).

[a] Predialysis vs. postdialysis, $P < 0.05$

[b] The post-dialysis value is significantly ($P < 0.05$) different from that in the dCa^{++} 1.25 hemodialysis

[c] The post-dialysis value is significantly ($P < 0.05$) different from that in the dCa^{++} 1.5 hemodialysis

mmol/liter, NS). During the $dCa^{++}1.5$ dialysis, serum-ionized calcium increased (1.24 ± 0.10 vs. 1.34 ± 0.06 mmol/liter, $P = 0.004$), and the postdialysis serum value was significantly ($P = 0.003$) higher than after the $dCa^{++}1.25$ dialysis. The $dCa^{++}1.75$ dialysis resulted in a marked increase in serum-ionized calcium (1.19 ± 0.10 vs. 1.47 ± 0.06 mmol/liter, $P = 0.002$), and the postdialysis mean serum-ionized calcium was significantly higher than after the $dCa^{++}1.25$ or $dCa^{++}1.5$ dialyses ($P = 0.002$ and $P = 0.003$, respectively). At the beginning of the study, the concentration of plasma intact PTH ranged from 1.6 to 42.2 (median 5.0) pmol/liter; only three patients had notably high plasma PTH values (higher than three times the upper limit of the reference range). The change in plasma PTH during the $dCa^{++}1.25$ HD (medians 5.0 vs. 7.2 pmol/liter, NS) or the $dCa^{++}1.5$ HD (medians 8.4 vs. 4.8 pmol/liter, NS) was not significant, whereas during the $dCa^{++}1.75$ HD, it decreased (medians 8.2 vs. 2.7 pmol/liter, $P = 0.002$). Both the predialysis values and the dialysis-induced changes in plasma phosphate, magnesium, sodium, potassium, chloride, creatinine, bicarbonate, pH, serum urea, and blood hemoglobin were equal in the three dialysis sessions, as shown in Table 2.

Echocardiographic findings

The Doppler and M-mode echocardiography data on the patient group, measured before the $dCa^{++}1.25$ HD, were compared with those on the control group (Table 3). The patient group had significantly thicker LV posterior wall (11.3 ± 1.5 vs. 8.0 ± 1.5 mm, $P < 0.01$) and interventricular septum (13.4 ± 2.1 vs. 8.9 ± 1.5 mm, $P < 0.01$) than the control group. LVESD (40.4 ± 4.1 vs. 29.7 ± 4.0 mm, $P < 0.01$) and LVEDD (58.4 ± 8.6 vs. 51.9 ± 3.3 mm, $P < 0.05$) were greater, and FS was smaller (31 ± 8 vs. 43 ± 5%, $P < 0.01$) in the patients. E_{max} (0.773 ± 0.172 vs. 0.610 ± 0.103 m/second, $P < 0.05$), A_{max} (0.669 ± 0.235 vs. 0.430 ± 0.072 m/second, $P < 0.01$), and IVRT (125 ± 26 vs. 78 ± 16 msecond, $P < 0.01$) were greater, and E/A_{max} was slightly (1.278 ± 0.514 vs. 1.448 ± 0.329, $P = 0.25$) smaller in patients than in controls.

There was a slight decrease in E_{max} during all dialysis

Table 3. M-mode and Doppler echocardiography data on the control subjects and patients, measured before (pre) and after (post) the three dialysis treatments

			Dialysate Ca^{++} 1.25 mmol/liter		Dialysate Ca^{++} 1.5 mmol/liter		Dialysate Ca^{++} 1.75 mmol/liter	
	Controls	*P*	pre	post	pre	post	pre	post
Emax *m/second*	0.610 ± 0.103	0.05	0.773 ± 0.172	0.648 ± 0.238	0.845 ± 0.09	0.669 ± 0.202[a]	0.795 ± 0.178	0.688 ± 0.187
Amax *m/second*	0.430 ± 0.072	< 0.01	0.669 ± 0.235	0.658 ± 0.282	0.712 ± 0.236	0.691 ± 0.303	0.733 ± 0.209	0.775 ± 0.263
E/Amax	1.448 ± 0.329	0.25	1.278 ± 0.514	1.118 ± 0.702	1.325 ± 0.616	1.081 ± 0.453	1.153 ± 0.437	0.943 ± 0.352[a,b]
IVRT *msecond*	78 ± 16	< 0.01	125 ± 26[d]	141 ± 33	147 ± 21	144 ± 29	147 ± 29	175 ± 50[a,b,c]
DT *msecond*	181 ± 32	0.38	179 ± 59	210 ± 79	174 ± 74	187 ± 63	176 ± 48	210 ± 91
LVEDD *mm*	51.9 ± 3.3	0.02	58.4 ± 8.6	54.9 ± 9.6[a]	56.4 ± 7.7	54.2 ± 8.4	55.4 ± 8.5	53.1 ± 9.0
LVESD *mm*	29.7 ± 4.0	< 0.01	40.4 ± 9.8	40.1 ± 8.0	42.1 ± 9.5	36.8 ± 13.3	38.0 ± 11.8	38.4 ± 10.9
FS %	43 ± 5	< 0.01	31 ± 8	29 ± 9	26 ± 9	27 ± 6	33 ± 12	29 ± 10
PWT *mm*	8.0 ± 1.5	< 0.01	11.3 ± 1.5	11.1 ± 1.7	11.7 ± 1.4	11.5 ± 2.2	11.7 ± 1.9	12.8 ± 2.2
IVST *mm*	8.9 ± 1.5	< 0.01	13.4 ± 2.1	14.0 ± 2.7	13.6 ± 1.5	13.4 ± 2.0	13.5 ± 2.4	13.7 ± 1.5
LA *mm*	34.8 ± 2.2	< 0.01	44.4 ± 6.1	41.0 ± 7.3[a]	43.0 ± 6.7	39.6 ± 5.2	45.1 ± 6.7	42.8 ± 5.7
AO *mm*	33.7 ± 4.4	0.16	35.9 ± 2.3	35.7 ± 2.5	35.9 ± 2.6	35.8 ± 2.4	36.9 ± 2.9	36.7 ± 2.4
LA/AO	1.0 ± 0.1	< 0.01	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.1	1.1 ± 0.1	1.2 ± 0.2	1.2 ± 0.2

Abbreviations are: Emax, peak early diastolic velocity; Amax, peak late diastolic velocity; E/Amax, Emax/Amax ratio; IVRT, isovolumic relaxation time; DT, deceleration time; LVEDD, left ventricle end diastolic dimension; LVESD, left ventricle end systolic dimension; FS, fractional shortening; PWT, posterior wall thickness; IVST, interventricular septal thickness; LA, left atrium dimension; AO, aortic root dimension; LA/AO, LA/AO ratio.

P Values denote controls vs. patients (the predialysis values of dCa^{++} 1.25 hemodialysis).

[a] Before vs. after hemodialysis, $P < 0.05$

[b] Postdialysis value is significantly ($P < 0.05$) different from that in the dCa^{++} 1.25 hemodialysis

[c] Postdialysis value is significantly ($P < 0.05$) different from that in the dCa^{++} 1.5 hemodialysis

[d] Predialysis value is significantly ($P < 0.05$) different from that in the dCa^{++} 1.5 and dCa^{++} 1.75 hemodialysis

treatments, but A_{max} remained unchanged. E/A_{max} decreased during HD in each session, suggesting impairment of LV relaxation, but only during HD with the dCa^{++}1.75 dialysate was the impairment statistically significant. The predialysis values of E/A_{max} were comparable between the three different procedures, but after the dCa^{++}1.75 dialysis, E/A_{max} was slightly smaller than after the dCa^{++}1.5 dialysis ($P = 0.07$) and was significantly smaller than after the dCa^{++}1.25 dialysis ($P < 0.05$). Similarly, the dCa^{++}1.75 HD was the only procedure during which IVRT increased significantly (147 ± 28 vs. 175 ± 49 msecond, $P < 0.05$). Predialysis IVRT in the dCa^{++}1.75 dialysis was greater than that with dCa^{++}1.25 dialysis but was comparable to that in the dCa^{++}1.5 dialysis. After the treatment, IVRT in the dCa^{++}1.75 dialysis was significantly greater than that in both the dCa^{++}1.25 and dCa^{++}1.5 dialyses. Also, DT tended to increase during each dialysis treatment, and the predialysis and postdialysis values were comparable between the three procedures.

Left ventricular end-diastolic dimension and left atrium dimension (LA) decreased during all dialysis treatments, the changes being significant in the dCa^{++}1.25 dialysis. FS, interventricular septum thickness, or posterior wall thickness did not change during any of the three HD sessions. All the indices of LV dimensions, wall thicknesses, and systolic function were comparable between the three procedures both before and after treatment.

When the Doppler indices of LV relaxation were compared with serum calcium levels before and after all three sessions, there were weak correlations between serum-ionized calcium and E_{max} ($r = -0.30$, $P < 0.05$), E/A_{max} ($r = -0.25$, $P < 0.05$), and IVRT ($r = 0.25$, $P < 0.05$). Plasma PTH did not correlate with any of the indices of pulsed Doppler or M-mode echocardiography. In a multiple regression analysis in which the total UF, the predialysis values of E/A_{max}, IVRT, FS, and LVEDD, and the changes in serum-ionized calcium, heart rate, and systolic and mean arterial blood pressure were independent variables, the change in serum Ca^{++} was the only variable correlating independently with the change in E/A_{max} ($r = -0.38$, $P < 0.05$).

DISCUSSION

We have previously shown that an acute rise in serum-ionized calcium concentration induced by calcium infusion impairs LV relaxation [8]. This study confirms that the changes in serum calcium concentration induced by HD also have an effect on cardiac relaxation. The term LV relaxation here comprises the energy- and calcium-dependent phase of early ventricular filling, and the term diastolic function merely represents the late phase of LV filling affected by the restrictive processes [23].

Left ventricular systolic function was poorer and LV wall thicknesses and dimensions greater in our patients with ESRD than in healthy control subjects, which is in agreement with previous reports [1–4, 6–8]. Our finding of a slight impairment of LV relaxation in ESRD patients is also supported by other studies [4, 5, 7].

None of the three dialysis treatments with a different concentration of dialysate calcium induced changes in

LV systolic function. This finding is compatible with those in previous studies [13, 15], which showed HD treatment with a rise in serum calcium concentration to have no effect on LV systolic function. It has been proposed that an HD procedure without fluid removal improves LV systolic function if serum Ca^{++} increases [10] or if, in addition to this, the plasma potassium concentration decreases [11]. In this study, we found no change in LV systolic function in spite of the alteration in the serum concentrations of the electrolytes. Our previous study demonstrated that LV systolic function is not altered, although the serum-ionized calcium concentration rises acutely [8]. Moreover, LV systolic function has been shown to be independent of acute changes in cardiac preload [17]. It therefore seems conceivable that an HD procedure or acute changes in serum calcium concentration do not have any significant effect on LV systolic function.

During HD, the cardiac preload decreases considerably as a result of fluid removal. Reduced preload has been shown to reduce LVEDD, E_{max}, and E/A_{max}, while having no effect on A_{max} [14, 16, 17]. During the interval between the HD sessions, the fluid retention, in turn, expands the circulating blood volume and thus increases cardiac preload, resulting in a "pseudonormalization" of Doppler indices of LV inflow. As a matter of fact, several studies have demonstrated a deterioration in LV diastolic indices during HD, but in all of these studies, the serum concentration of calcium increased significantly during dialysis [13, 15, 16]. Therefore, although the adverse effects of reduced preload on LV diastolic indices during HD treatment are obvious, it has hitherto been impossible to distinguish whether the changes in serum calcium concentration have a separate effect on LV relaxation properties during an HD procedure.

There was a trend toward impairment of LV relaxation (a decrease in E/A_{max} and an increase in DT and IVRT) during all treatments. However, E/A_{max} and IVRT changed significantly only during the $dCa^{++}1.75$ dialysis, that is, when serum-ionized calcium increased significantly. This finding goes well with that of our recent study, which showed induction of acute hypercalcemia to impair LV relaxation [8]. All of this may indicate that although the Doppler indices of LV inflow decrease during HD treatment as a reflection of reduced cardiac preload, a significant deterioration in LV relaxation during an HD procedure takes place only if there is a simultaneous and marked increase in serum-ionized calcium concentration. The impairment of LV relaxation during the $dCa^{++}1.75$ HD did not induce any notable clinical symptoms in our patients. However, the predialysis echocardiographic indices showed our patients to have only mild LV dysfunction at the baseline, and it may be that the risk of clinical consequences is greater in ESRD patients with more compromised cardiac function.

E_{max} is known to be reduced along with an increase in cardiac afterload [24]. Some researchers have reported both systolic and mean arterial blood pressure to increase during high-calcium dialysis [25, 26], whereas other studies have shown blood pressure to remain stable during high-calcium HD [13, 15, 16] or acute induction of hypercalcemia [8]. In this study, systolic and mean arterial blood pressure tended to rise during the $dCa^{++}1.75$ HD, but the changes did not reach statistical significance during any session. LV relaxation is also affected by changes in heart rate [27] and cardiac preload [14, 16, 17]. However, in our study, the predialysis and postdialysis values and the dialysis-induced changes in systolic and mean arterial blood pressures, heart rate, mean body weight, and the total UF were comparable between the three HD procedures. In a multiple regression analysis containing the previously mentioned variables, serum-ionized calcium and the predialysis values of E/A_{max}, IVRT, FS, and LVEDD, the dialysis-induced change in E/A_{max} correlated independently only with serum Ca^{++}. Similarly, there were no differences in the predialysis or postdialysis concentration of plasma phosphate, magnesium, sodium, potassium, chloride, creatinine, pH, bicarbonate, serum urea, or blood hemoglobin between the different sessions. Thus, the impairment of LV relaxation during only the $dCa^{++}1.75$ dialysis cannot be explained by the changes in these variables.

During HD, serum-ionized calcium is directly related to the dialysate calcium concentration, and changes in Ca^{++} in turn induce a suppression or stimulation of parathyroid function [18, 19]. This makes it difficult to separate the distinct effects of serum calcium and PTH on cardiac function during HD. Myocardial contraction and relaxation are highly dependent on cytosolic calcium homeostasis [20], and PTH has been shown to affect this homeostasis [22]. Several studies have shown secondary hyperparathyroidism to be at least partly responsible for the high prevalence of cardiac dysfunction and LV hypertrophy in patients with chronic renal failure [2, 6, 7, 28, 29]. Nevertheless, in this study, plasma PTH did not correlate with any echocardiographic indices of LV structure or function, whereas serum-ionized calcium correlated inversely with E_{max} and E/A_{max} and positively with IVRT. A corresponding relationship between LV relaxation and an acute change in serum-ionized calcium, but not plasma PTH, was found in our previous study [8]. Thus, although the long-term adverse effects of chronic renal failure on cardiac structure and function may be at least partly due to chronic excess of PTH, the acute changes in LV relaxation that occur, for example, during HD treatment, may be predominantly due to changes in serum-ionized calcium.

In conclusion, we found that in patients with ESRD, HD with high-calcium dialysate ($dCa^{++}1.75$ mmol/liter) impairs LV relaxation when compared with lower cal-

cium dialysate (dCa^{++}1.25 mmol/liter or dCa^{++}1.5 mmol/liter) treatments. This finding may be of clinical importance when treating patients with compromised cardiovascular system.

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APPENDIX

Abbreviations used in this article are: A_{max}, peak late diastolic velocity; dCa^{++}1.25, dialysate Ca^{++} concentration of 1.25 mmol/liter; dCa^{++}1.50, dialysate Ca^{++} concentration of 1.5 mmol/liter; dCa^{++}1.75, dialysate Ca^{++} concentration of 1.75 mmol/liter; DT, deceleration time; E_{max}, peak early diastolic velocity; HD, hemodialysis; IVRT, isovolumic relaxation time; LA, left atrium; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; PTH, parathyroid hormone; UF, ultrafiltration.

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